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Depressive Symptoms as Predictors of Mortality in Patients With COPD*

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Objective: Prognostic studies of mortality in patients with COPD have mostly focused on physiologic variables, with little attention to depressive symptoms. This stands in sharp contrast to the attention that depressive symptoms have been given in the outcomes of patients with other chronic health conditions. The present study investigated the independent association of depressive symptoms in stable patients with COPD with all-cause mortality.

Methods: The baseline characteristics of 121 COPD patients (78 men and 43 women; mean [\pm SD] age, 61.5 \pm 9.1 years; and mean FEV₁, 36.9 \pm 15.5% predicted) were collected on hospital admission to a pulmonary rehabilitation center. The data included demographic variables, body mass index (BMI), post-bronchodilator therapy FEV₁, and Wpeak (peak workload [Wpeak]). Depressive symptoms were assessed using the Beck depression inventory. The vital status was ascertained using municipal registrations. In 8.5 years of follow-up, 76 deaths occurred (mortality rate, 63%). Survival time ranged from 88 days to 8.5 years (median survival time, 5.3 years). The Cox proportional hazard model was used to quantify the association of the baseline characteristics (*ie*, age, sex, marital status, smoking behavior, FEV₁, BMI, Wpeak, and depressive symptoms) with mortality.

Results: Depressive symptoms (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.12 to 3.33) were associated with mortality in patients with COPD, independent of other factors including male sex (OR, 1.73; 95% CI, 1.03 to 2.92), older age (OR, 1.05; 95% CI, 1.02 to 1.08), and lower Wpeak (OR, 0.98; 95% CI, 0.97 to 0.99).

Conclusions: This study provides evidence that depressive symptoms assessed in stable patients with COPD are associated with their subsequent all-cause mortality. (CHEST 2009; 135:619–625)

Key words: COPD; depression; psychology; pulmonary rehabilitation; smoking

Abbreviations: BDI = Beck depression inventory; BMI = body mass index; CI = confidence interval; OR = odds ratio; Wpeak = peak workload

In the last few decades, there has been a global increase in mortality from COPD, which is expected to be the third most frequent cause of death by the year 2020.¹ Studies predicting mortality in patients with COPD have mainly focused on physiologic variables, and only occasionally on psychological variables. Airflow limitation (FEV₁),^{2,3} hypercapnia,⁴ hypoxemia,⁵ increased dyspnea,⁶ and poor nutritional status^{7,8} have all been found to be risk factors for mortality in COPD patients. Also, variables such as reduced Wpeak,^{9,10} poor health-related quality of life,¹¹ and living without a partner¹² were found to be associated with increased mortality. Celli and coworkers¹³ proposed a multidimensional grading system, consisting of graded scores of body mass

index (BMI), airflow obstruction, dyspnea and Wpeak (or BODE index), and they have found that it is a useful tool for predicting the risk of death in COPD patients.

Depressive symptoms are prevalent among COPD patients, but have not been given much consideration as prognostic factors, despite their having been associated with higher mortality in other diseases,^{14–17} as well as with all-cause mortality. For example, Frasure-Smith and coworkers¹⁸ demonstrated that both subclinical depressive symptoms and major depression are related to mortality in patients after myocardial infarction.

Estimates of the prevalence of depression and depressive symptoms tend to be high among COPD

patients, varying from 6 to > 60%.^{19–21} This large variance in estimates can be attributed to differences in sampling, but particularly to variability in the instruments and cutoff scores used to measure depression, as well as a conflation of elevations in self-reported depressive symptoms with the less prevalent and less commonly studied psychiatric diagnosis of depression.²⁰

Some studies have demonstrated only a weak association between psychological disturbance²² or health-related quality of life¹¹ and mortality in COPD patients. Yet, depressive symptoms were found to be strong predictors for mortality (odds ratios [ORs], 1.9,²³ 3.6,²⁴ and 2.7²⁵), independent of other disease severity and other risk factors, in COPD patients in three studies. It is noteworthy that two of the studies^{23,24} focused on COPD patients who had been hospitalized for acute exacerbation. The assessment of the depression symptoms was conducted during or shortly after (within 2 to 4 weeks) hospitalization for an exacerbation, which may have been reflected in increased the levels of depressive symptomatology. Only one study²⁵ demonstrated that adjusted depressive symptoms were associated with 3-year mortality and not with 1-year mortality in stable COPD patients. In contrast, two other studies^{26,27} did not find an association between mortality and depression after adjustment for disease severity. These conflicting data raise the question of whether depression symptoms are also related to mortality in a group of clinically stable patients with COPD. This question became the basis for the present study, which investigated the association of depressive symptoms and all-cause mortality in stable patients with COPD, adjusting for known risk factors such as age, marital status, smoking, BMI, Wpeak and FEV₁ percent predicted.

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MATERIALS AND METHODS

Subjects

Our study sample consisted of 121 consecutive stable patients, all with COPD (FEV₁ < 80% predicted) that had been diagnosed according to the American Thoracic Society guidelines,²⁸ who were referred for pulmonary rehabilitation between September 1998 and March 2000. All patients had been clinically stable for at least 6 weeks and did not require an increase in medication or hospitalization. Exclusion criteria were the inability to perform lung function tests and/or ergometry, refusal to fill out psychological questionnaires, and the presence of a comorbidity such as malignancy or severe heart failure, that limits the prognosis.

Measurements

Patient Characteristics: On hospital admission, demographic data, such as sex, age and marital status were recorded. Marital status was dichotomized into the following two groups: living with a partner and living without a partner. Patients without a partner included those patients who had never married, or were separated or widowed. Smoking behavior was assessed by a self-report questionnaire and was placed in one of the following two categories: (0) never had smoked cigarettes or had been an ex-smoker for ≥ 1 year; and (1) current smoker or had been an ex-smoker for < 1 year.

Depression: The presence of depressive symptoms was assessed with the original Beck depression inventory (BDI) I.^{29,30} The BDI-I is a 21-item self-administered rating inventory measuring attitudes and symptoms of depression. It takes approximately 10 min to complete. Total score ranges from 0 to 63, with a higher score indicating more pathology. The scale has high internal consistency, and good discriminant and convergent validity.³⁰ In the present article, we studied the impact of depressive symptoms on mortality, but not the impact of major depressive disorder. In our analyses, we used the recommended cutoff level for clinically significant depressive symptoms in otherwise healthy individuals (*ie*, BDI score ≥ 19 ³¹) to define the high/low depressive symptoms distinction.

Physiologic Parameters: The BMI is reported as the weight in kilograms divided by the square of the body height in meters. Airflow obstruction was established by the FEV₁, post-bronchodilator therapy, expressed in liters and as a percentage of the predicted value, and was assessed (Masterlab 4.521 plethysmograph; Jaeger; Würzburg, Germany) according to American Thoracic Society standards.²⁸ Arterial blood gas levels at rest, PaO₂, and PaCO₂, were assessed while the patient was breathing room air. Exercise capacity (*ie*, peak workload [Wpeak]) was defined as the highest workload reached and was maintained for at least 30 s during symptom-limited incremental cycle ergometry testing (Oxycon pro; Cardinal Health; Dublin, OH).³² A protocol with a 5 or 10 W/min increment in load was applied depending on the estimated Wpeak, starting with 1 min of unloaded pedaling and aiming at a duration of 6 to 12 min.

Mortality: The vital status of these patients was ascertained on April 1, 2007, using municipal registrations. The rationale for relying on all-cause mortality was that clinical assessments of the cause of death are difficult to obtain, often incorrect, and always involve a subjective judgement.³³

Statistical Analysis

All analyses were performed using a statistical software package (SPSS, version 12.0.1 for Windows; SPSS Inc; Chicago, IL). All 121 patients were included in the main analyses. However,

Table 1—Characteristics of the COPD Patients*

Variables	All Patients (n = 121)
Male sex, %	65
Age, yr	61.5 ± 9.1
With Partner, %	70
Smoking, %	
NS or ES ≥ 1 yr	52
CS or ES < 1 yr	48
FEV ₁	
L	1.09 ± 0.54
% predicted	36.9 ± 15.5
GOLD stages II/III/IV, %	18.2/41.3/40.5
BMI, kg/m ²	25.5 ± 6.0
W _{peak} , W	58.7 ± 33.6
PaO ₂ ,† kPa	9.3 ± 1.7
PaCO ₂ ,† kPa	5.3 ± 0.8
Depression BDI score	12.6 ± 8.2
High depressive symptoms (BDI score ≥ 19), %	20
Mortality rate, %	63
Median follow-up time for all patients, yr	5.3
Median follow-up time for survivors, yr	7.8
Median follow-up time for patients who died, yr	3.0

*Values are given as the mean ± SD, unless otherwise indicated. NS = never-smoker; ES = ex-smoker; CS = current smoker; GOLD = Global Initiative for Chronic Obstructive Lung Disease. †n = 102.

additional analyses focused on the subsample of 102 patients for whom PaO₂ and PaCO₂ data were available. Continuous variables are presented as the mean ± SD, except for follow-up time, which is presented as the median. Dichotomized variables are presented in percentages. The relations between the variables were presented as Pearson correlations for continuous variables and ϕ correlations for dichotomous variables. Univariate hazards (ORs) associated with each variable were examined. Multivariate Cox proportional hazard analyses with a stepwise forward likelihood ratio method including all variables were used to quantify the relationship between baseline variables and mortality and 95% confidence intervals (CIs) were estimated with significance

set at $p < 0.05$. High/low depressive symptoms were plotted in survival curves using Kaplan-Meier estimates.

RESULTS

The characteristics of the patients (78 men and 43 women) are presented in Table 1. The mean age was 61.5 ± 9.1 years. Their post-bronchodilator therapy FEV₁ was $36.9 \pm 15.5\%$ predicted. With regard to depression, 19.8% of patients tested above the standard cutoff score of ≥ 19 and were classified as having moderate-to-severe depressive symptoms.

Of the 121 patients who participated in the study, 76 (63%) had died at the end of the study. The median survival time for all patients was 5.3 years. The median survival time for the patients who died was 3.0 years (survival range, 88 days to 7.8 years). The median survival time for the 45 patients (37%) who were alive at the end of the study was 7.8 years (survival range, 7.1 to 8.5 years).

Table 2 shows the correlations among key predictor variables. High depressive symptoms are not correlated with any of these variables except for continued smoking behavior ($r = 0.27$).

Table 3 shows the results of the Cox proportional hazard analyses. On a univariate level, male gender, older age, a lower W_{peak}, and high depressive symptoms are significantly related to mortality in COPD patients.

These variables were entered into the multivariate analysis. We found that high depressive symptoms are significantly associated with mortality, independent of male gender, older age, and lower W_{peak}. High depressive symptoms nearly double the mortality risk in COPD patients when compared to low depressive symptoms (OR, 1.93; 95% CI, 1.12 to 3.33). In a subsample of 102 patients for which both PaO₂ and PaCO₂ data were available, we found that neither variable was correlated with depressive

Table 2—Correlations Between Possible Predictors for Mortality in COPD Patients (n = 121)*

Variables	1	2	3	4	5	6	7	8
1. Sex (0 = female)	1							
2. Age in yr	0.22†	1						
3. Partner (0 = no)	0.23†	−0.01	1					
4. Smoking‡	−0.08	−0.03	−0.21†	1				
5. FEV ₁ (L)	0.24§	−0.23†	0.23§	−0.12	1			
6. FEV ₁ (% predicted)	−0.04	−0.08	0.15	−0.11	0.90§	1		
7. BMI	−0.13	−0.10	0.11	−0.22†	0.29§	0.34§	1	
8. W _{peak}	0.03	−0.35§	0.24§	−0.14	0.53§	0.40§	0.34§	1
9. Depressive symptoms (0 = low)	−0.06	−0.06	−0.18	0.27§	−0.04	−0.01	−0.10	−0.17

*All correlations are Pearson correlations except for dichotomous variables, where ϕ correlations were used. See Table 1 for abbreviations not used in the text.

† $p < 0.05$.

‡0 = NS or ES for ≥ 1 year; 1 = CS or ES for < 1 year.

§ $p < 0.01$.

Table 3—Predictors for Mortality in COPD patients, Cox Proportional Hazard Model Stepwise Forward Likelihood Ratio Method

Variables	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Sex (0 = female)	1.67	1.02–2.73*	1.73	1.03–2.92*
Age in years	1.07	1.05–1.11†	1.05	1.02–1.08†
Partner (0 = no)	0.67	0.42–1.07		
Smoking	1.38	0.88–2.17		
FEV ₁ % predicted	0.99	0.97–1.01		
BMI	0.96	0.92–1.00		
Wpeak	0.98	0.97–0.99†	0.98	0.97–0.99†
Depressive symptoms (0 = low)	1.78	1.06–3.00*	1.93	1.12–3.33*

*p < 0.05.

†p < 0.001.

symptoms. Only lower PaO₂ was associated with mortality in the univariate analysis (OR, 0.98; 95% CI, 0.96 to 0.99), but not in the multivariate analysis. PaCO₂ was not associated with mortality in either univariate or multivariate analyses. In this smaller sample, high depressive symptoms remained significantly associated with mortality. We did not find any significant interaction effects. In Figure 1, survival curves using the Kaplan-Meier estimates are plotted for the two groups (*ie*, those patients with high depressive symptoms and those with low depressive symptoms).

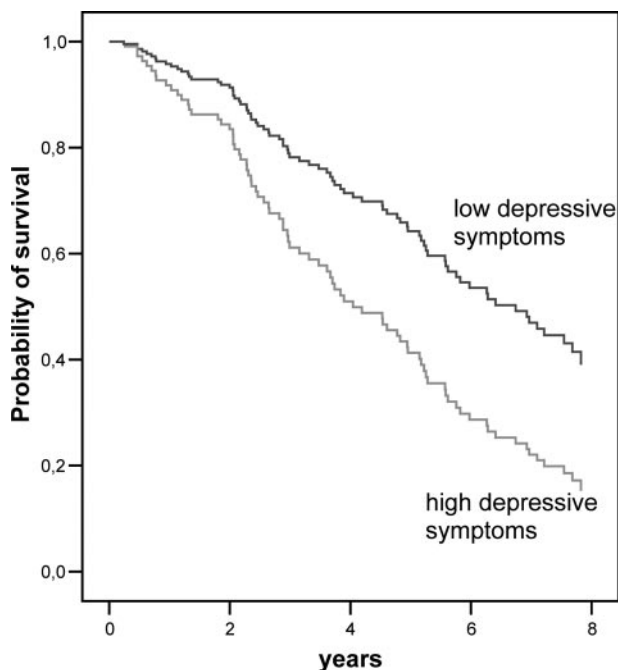


FIGURE 1. Kaplan-Meier curves for COPD patients with separate lines for high and low depressive symptoms (adjusted for the covariates sex, age, and Wpeak).

DISCUSSION

This study provides preliminary evidence that depressive symptoms are an independent prognostic factor for mortality among stable COPD patients, even when adjustments are made for risk factors such as age, sex, and Wpeak. The association of depressive symptoms and mortality has been demonstrated in COPD patients assessed during or shortly after hospitalization for an exacerbation. However, to our knowledge, this is one of the first studies demonstrating that there is an association even in stable COPD patients. We observed this association among clinically stable COPD patients who had been referred for pulmonary rehabilitation, which perhaps limits generalization to all COPD patients. However, we believe that our results are even more compelling because our patient group was, on average, 10 years younger than the patients in the earlier studies.^{23,24} The younger age and the large number of deaths observed in our sample make it more than plausible that age and age-related morbidities are not the only contributing factors. Our study is in line with and strengthens the evidence in the recently published paper by Fan and coworkers,²⁵ which demonstrated the adjusted risk of 3-year mortality among stable COPD patients with BDI scores ≥ 15 . The results of our study are also in line with those from studies conducted in different patient groups. For instance, in elderly hospitalized patients with several medical conditions¹⁴ and in patients after myocardial infarction,^{17,18} a modest-to-strong association between depression and mortality has been demonstrated.

It is noteworthy that in the assessment of depression in patients with cardiovascular disease, some sources have argued^{34–37} that depressive symptoms obtained with instruments like the BDI are inflated among patients with medical disease because of the confounding of vegetative symptoms. This has motivated Beck et al³⁸ to revise the original BDI and create the BDI-II. However, few studies have actually examined this question with appropriate methodologies for detecting differential item functioning. Simon et al³⁹ looked at somatic and nonsomatic depressive symptoms among depressed managed care patients with diabetes, ischemic heart disease, and COPD compared to patients without chronic disease. They found only very minor deviations in symptom reporting and found that all four *Diagnostic and Statistical Manual of Mental Disorders* IV somatic symptoms improved with treatment of depression regardless of whether or not patients had comorbid medical illness. Instruments, such as depression subscale of the hospital anxiety and depression scale, which are constructed to avoid the assess-

ment of somatic symptoms, have not been shown to be superior to conventional instruments for assessing depression, such as the BDI.^{40,41} As with the hospital anxiety and depression scale, the BDI is not a diagnostic case finder for major depressive disorder. However, on an individual level, a high score can be used as a suitable indication for follow-up assessment.

Some possible explanations can be offered for the finding that depressive symptoms have prognostic value in COPD patients. First, some studies^{42–44} have demonstrated that depression can affect the hypothalamic-pituitary-adrenal axis functioning, which could make health status deteriorate. Second, depressive symptoms can impair self-care, as indicated by insufficient nutritional intake, continued smoking, lower activity levels, poor medication compliance, and initiation of an action plan for exacerbation in addition to less adequate health-care seeking, which also could lead to an accelerated decline in health. In our study, we did not have data on hypothalamic-pituitary-adrenal axis functioning or follow-up data on behavioral factors. We suggest that such data be collected in future studies.

In our sample, depressive symptoms were independent of other known risk factors, except that depressive symptoms were correlated with continued smoking or recent smoking cessation. However, smoking behavior is not related to mortality in this sample, which frustrates a search for mechanism. We attempted to control for the influence of a number of risk factors known to predict mortality, but our list could have been incomplete and our measurement imperfect. It has been suggested⁴⁵ that the wide range of conditions for which depressive symptoms have been shown to predict mortality suggests either a very general susceptibility or that confounding is at play. Moreover, similar to other health conditions in which depressive symptoms have been shown to predict mortality, it has yet to be demonstrated that improvement in depressive symptoms will yield decreased mortality. It is common a call for intervention to be made when depressive symptoms are observed to have a predictive value for mortality. But, the empirical basis for that call is not typically provided.

Some limitations of this study should be noted. First, the data on the nature and numbers of comorbid conditions were not consistently recorded and therefore were not included in the study. Data on comorbidities could have provided us with additional clues on a possible explanatory mechanism of the association between depressive symptoms and mortality. Second, the cause of death was not determined, so we studied all-cause mortality and not just respiratory causes of death. The cause of death is

sometimes hard to establish, in particular when patients die at home; death certificate data on the actual cause of death are not independently validated and are known to be less trustworthy.³³ Third, our study includes potentially modifiable risk factors such as smoking behavior, BMI, Wpeak, and depressive symptoms that may change in the course of time. Also, we have no data on the prescription of antidepressants. The use of antidepressants might have influenced our assessment of depressive symptoms by lowering symptoms. However, most depression in medically ill patients goes unrecognized or is inadequately treated, and the effects on depressive symptoms are further limited by poor patient adherence to treatment and poor physician follow-up. Nonetheless, future research should include assessment of patients' receipt of antidepressants and psychological treatment. Alterations in behavior, interventions, or hospitalizations may affect prognosis. However, we do not have follow-up data on psychological or physiologic variables in our sample, or on the effects of treatment during or after rehabilitation. Although it is known that pulmonary rehabilitation may improve recognized predictors of mortality such as Wpeak, dyspnea, and quality of life, there is no evidence yet that pulmonary rehabilitation is beneficial with regard to survival.⁴⁶ Further observational studies of the correlates of depressive symptoms and their specific components such as hopelessness⁴⁷ or somatic complaints⁴⁸ are needed before proposing interventions. Finally, the assessment of depressive symptoms in our study was limited to a single point in time. This assessment allowed a preliminary demonstration of the value of assessing such symptoms, but leaves unexplored questions about their stability or trajectory over time, and particularly how changes in these symptoms are related to changes in morbidity and mortality. Taken together with findings of the few other studies demonstrating the predictive value of depressive symptoms in COPD, our results give encouragement to more ambitious studies of the course of depressive symptoms in relation to mortality.

In conclusion, this study demonstrates the association of high levels of depressive symptoms in COPD patients with mortality after adjustment for known risk factors such as sex, age, and Wpeak. What is needed next is the explication of both the determinants of depressive symptoms, and the pathway between these symptoms and mortality.

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